

### **REMARKS/ARGUMENTS**

Claims 1, 3, 8-9, 13-15, 17-18 and 21-23 are pending in the above-identified application. The specification is amended to capitalize each letter of any trademarks, as well as to include the proper trademark symbol and to include generic terminology for these trademarks. The specification is also amended to correct certain obvious typographical errors. No new matter is added by these amendments. In light of these amendments and the remarks and arguments set forth below, Applicants respectfully request reconsideration of the application.

### **Objections to the Specification**

The specification stands objected to for the use of trademarks. The specification has been amended to capitalize each letter of the trademarks TEFLON® and PLASBUMIN™, as well as to include the corresponding generic terminology for TEFLON® ("polytetrafluorethylene (PTFE)"). Applicants note that the generic terminology for PLASBUMIN™ ("human serum albumin" or "HSA") is already recited wherever "PLASBUMIN™" appears. The specification is further amended to include the registered trademark symbol "®" wherever previously omitted. (See paragraphs [0078], [0079], and [0085].) Also, the generic term "culture medium" has been inserted as appropriate for the trademarks X-VIVO-15® and AIM-V®. In view of these amendments, withdrawal of the objection is respectfully requested.

### **Art Rejections**

Applicants acknowledge the Examiner's withdrawal of the rejection of the claims as allegedly obvious over Sallusto and U.S. Patent Application Publication 2005/0173315. With the exception of this withdrawn rejection, the Examiner has maintained all previous art rejections under 35 U.S.C. §§ 102 and 103. For the reasons set forth further herein, in addition to reasons previously of record, cases of anticipation and obviousness have not been established with respect to the present claims. In particular, to further show novelty and non-obviousness of the claimed method, Applicants submit herewith the Declaration of Marnix Bosch under 37 C.F.R.

§ 1.132 (hereinafter the "Bosch Declaration"), which addresses the Examiner's remarks in the Office Action and shows that the cited references would not have led one of skill in the art to the present invention. Each of the presently maintained art rejections are addressed in turn below, with reference to the Bosch Declaration.

**Rejections under 35 U.S.C. § 102**

The Examiner contends that Sallusto anticipates claims 1, 14, 17-19, and 23 under 35 U.S.C. § 102. The Examiner, citing to Table 1 of Sallusto, alleges that Sallusto teaches "a method for generating dendritic cells from peripheral blood mononuclear cells (i.e., monocytic dendritic cell precursors) by culturing GM-CSF in the absence of additional cytokines," and further asserts that Sallusto's dendritic cells are "immature, as evidenced by their expression of CD11c and MHC, but lack of expression of B7." (Office Action at p. 3.) Contrary to the Examiner's remarks regarding Sallusto as summarized above, Sallusto does not disclose a method for generating dendritic cells from monocytic dendritic cell precursors by culturing the cells in GM-CSF in the absence of additional cytokines (Bosch Declaration at ¶ 9), for reasons discussed further below.

First, as described in Sallusto, the identification of cells as dendritic cells ("DCs") "was based on three well-established and accepted criteria," including, *inter alia*, "their surface phenotype, with high expression of CD1, MHC class I and class II, Ii, FcγRII, B7, CD40, ICAM-1, LFA-3, and CD11c." (Bosch Declaration at ¶ 10 (citing Sallusto).) Thus, per Sallusto, cells not exhibiting surface expression of one or more of these markers are not considered to be DCs. (Bosch Declaration at ¶ 10.) Indeed, as Sallusto indicates, Sallusto's criteria for identification of DCs, including the criteria for surface marker expression, are criteria that have been well-established and accepted in the art. (*Id.* at ¶ 11.) Thus, a person of ordinary skill in the art, reading Sallusto, would recognize that cells not meeting one or more of these criteria are not DCs. (*Id.*)

Per Sallusto's own criteria as well as criteria well-established in the art for identification of DCs, as summarized above, Sallusto's "GM-CSF-only" cells are not dendritic cells, in contrast to those cells obtained by methods as disclosed and claimed in the present application. (Bosch Declaration at ¶ 16.) First, an examination of the data from Table 1 of Sallusto clearly shows that cells cultured with GM-CSF, but in the absence of additional cytokines, were negative for CD1. (*Id.* at ¶ 12.) Table 1 further shows that B7 expression was equivocal ("±"), and not positive ("+"), for cells cultured with GM-CSF without additional cytokines. (See Sallusto at p. 1112, Table 1, "GM-CSF" column.) This is in contrast to those cells cultured with GM-CSF and IL-4, which, in addition to expression of other DC phenotypic markers, exhibited both CD1 and B7 expression. (*Id.* (citing Sallusto).)

With regard to the Examiner's acknowledgment that Sallusto's GM-CSF-only cells "lack ... expression of B7," to the extent that the Examiner suggests that lack of B7 expression is a feature characteristic of immature dendritic cells, the Examiner has set forth an interpretation of Sallusto that is incorrect in view of the knowledge in the art. (Bosch Declaration at ¶ 13.) While B7 expression is upregulated in dendritic cells upon maturation, it was well-known as of the applications' filing date that dendritic cells also express B7 in their immature form. Indeed, this knowledge in the art is reflected in the Sallusto reference itself, as discussed above with respect to the DC surface phenotype. (*Id.*) Consistent with the knowledge in the art that immature dendritic cells express B7, the '807 application shows surface expression of B7 molecules (CD80 and CD86) on immature dendritic cells obtained by the methods of the present invention, as shown in, *e.g.*, Examples 3 and 6 and corresponding Figures 4 and 8, respectively. (*Id.* at ¶ 14.) In any event, irrespective of B7 expression, because Sallusto's GM-CSF-only cells also clearly lack expression of the dendritic cell marker CD1, including CD1a (*see* Sallusto at Table 1), it is clear that these cells are not immature DCs. (*Id.* at ¶ 15.) In this respect, and in contrast to Sallusto's GM-CSF-only cells, the immature dendritic cells of the present application were shown to express CD1a in addition to B7. (*Id.* (citing '807 application).)

Moreover, consistent with Sallusto's own criteria as well as criteria well-established for identification of DCs, Sallusto does not state that the GM-CSF-only cells are DCs. In contrast, Sallusto does explicitly state that GM-CSF/IL-4-expanded cells were identified as DCs. (Bosch Declaration at ¶ 17 (citing Sallusto).) The notable lack in Sallusto of any explicit statement equating the GM-CSF-only cells with DCs would reasonably be viewed by the skilled artisan as Sallusto's own acknowledgement that the GM-CSF-only cells are not DCs. (Bosch Declaration at ¶ 17.)

Indeed, Sallusto states that "[o]ur DC lines were generated from adult peripheral blood and require IL-4 in addition to GM-CSF to maintain the immature, antigen presenting competent state." (Sallusto at p. 1114, 2nd col., last para., bridging to p. 1115, 1st col. (emphasis provided).) In this regard, with respect to the Examiner's statement that "the instant method is a method of differentiating immature dendritic cells, and not a method of maintaining immature dendritic cells" (Office Action at p. 3), to the extent that the Examiner is suggesting by this statement that Sallusto's DCs were obtained without culture in IL-4, the Examiner's statement is inconsistent with any reasonable interpretation of Sallusto that would be reached by the skilled artisan reading this reference. (Bosch Declaration at ¶ 18.) Sallusto is concerned with the establishment of DC cell lines and clearly states that IL-4 was used in conjunction with GM-CSF to establish these cells lines. (*Id.* (citing Sallusto).) Sallusto sets forth various culture conditions that were tested for differentiation and expansion of DCs. In describing conditions for the "generation" of DCs, Sallusto discloses that adherent or light density PBMC fractions were cultured with the various combinations of GM-CSF, IL-4, and TNF- $\alpha$ . Sallusto further states that "a combination of GM-CSF and IL-4 provided the best conditions for the generation of cells with the characteristic phenotype and functional properties of DCs ...." (Bosch Declaration at ¶ 18 (citing Sallusto).) In view of this disclosure, the skilled artisan would reasonably understand that Sallusto's method for obtaining and maintaining DCs required IL-4 throughout the entire culture period, including during differentiation from PBMCs. (Bosch Declaration at ¶ 18.)

With respect to the Examiner's statement that the instant claims "are not limited to an immature dendritic cell that expresses CD1a or B7" (Office Action at p. 3), to the extent that the Examiner is suggesting that there is a class of immature dendritic cells that do not express CD1a or B7, such a suggestion is wholly inconsistent with any definition or characterization of immature dendritic cells accepted in the art as of the application's filing date. (Bosch Declaration at ¶ 19.) As discussed previously, according to Sallusto as well as the art-accepted criteria for identification of DCs, dendritic cells, by definition, express CD1a and B7, in addition to other characteristic surface markers. For this reason, a person of ordinary skill in the art, reading the instant '807 claims in light of the application, would reasonably understand that cells lacking CD1a and/or B7 expression, such as Sallusto's GM-CSF only cells, are not immature dendritic cells within the meaning of the instant claims. (*Id.*) In this regard, Applicants note that "the broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach." MPEP § 2111 (emphasis provided; citing *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999)).

With regard to the Examiner's statement that "Sallusto have performed the exact steps of the instantly claimed method and therefore must have inherently obtained an immature dendritic cell" (Office Action at p. 3), this statement is incorrect for at least two reasons. (Bosch Declaration at ¶ 20.) First, for the reasons already discussed above, Sallusto did not obtain immature dendritic cells using GM-CSF in the absence of additional cytokines. Second, Sallusto does not disclose the "exact" steps as presently claimed, for at least the reasons further discussed below. (*Id.* at ¶ 20.)

Independent claim 1 specifies that the monocytic dendritic cell precursors be "non-activated." (See Claim 1). As taught by the specification, methods typically used to enrich cell populations for dendritic cell precursors can activate the precursor cells, initiating terminal differentiation of the cells into, for example, macrophage. (Bosch Declaration at ¶ 21 (citing '807 application).) Such activation-inducing methods included, for example, the adherence of cells to plastic. (Bosch Declaration at ¶ 21 (citing '807 application).) In this regard, the skilled artisan would recognize that Sallusto's method includes cell adherence to plastic, and thus

includes activation of dendritic cell precursors. (Bosch Declaration at ¶ 22.) In particular, Sallusto's cells were isolated either by adherence of PBMC's to plastic or by depletion of B and T lymphocytes from "light density fractions." (*Id.* (citing Sallusto at p. 1110, 1st col., 3rd para.)). With respect to the "light density fractions," the skilled artisan would readily understand that these cells are monocytes isolated by density gradient centrifugation and that, even if the cells are not further purified by adherence, they would adhere to the plastic substrate (*e.g.*, polystyrene flasks) used for subsequent tissue culture. (Bosch Declaration at ¶ 22.) Further, the addition of other cytokines such as, *e.g.*, IL-4 or TNF- $\alpha$ , as used in previous methods, are believed to counter the effects of the isolation-associated activation of cells. (*Id.* at ¶ 23 (citing '807 application)). By using non-activated precursors, as presently claimed, the need for additional cytokines is bypassed. (Bosch Declaration at ¶ 23 (citing '807 application)). Sallusto's observations that IL-4 was required for generating dendritic cells from isolated precursors (as discussed above) are consistent with the specification's teachings that additional cytokines are needed with activated dendritic cell precursors, but not with non-activated precursors. (Bosch Declaration at ¶ 23.) Accordingly, Sallusto does not disclose a method using non-activated monocytic dendritic cell precursors, as presently claimed. (*Id.* at ¶ 24.)

For at least the reasons above, a person of ordinary skill in the art would not reasonably interpret Sallusto as disclosing "a method for generating dendritic cells from non-activated monocytic dendritic cell precursors by culturing GM-CSF in the absence of additional cytokines." (Bosch Declaration at ¶ 25.)

With regard to claims 17 and 18, while these claims are novel for at least the reasons above, Applicants further disagree with the Examiner's inclusion of these claims in the present rejection on the basis that the instant method "is drawn to a method of differentiating monocytic precursors and not to a method of enriching precursors" (Office Action at p. 4). According to the Examiner, "the manner in which the precursors are obtained does not carry any patentable weight in the absence of [a] structural difference." The Examiner goes on to state that "precursors enriched by tangential flow filtration would be the same as the precursors of Sallusto *et al.*" (*Id.*)

In response to the Examiner's assertions quoted above, Applicants first note that for a reference to anticipate a claim under 35 U.S.C. § 102, the reference must expressly or inherently disclose each and every limitation recited in the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Therefore, the reference must disclose the "identical invention ... in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Each and every limitation as recited in the claim must be considered. *See* MPEP § 2131. Here, claims 17 and 18 require that the dendritic cell precursors be "further enriched by tangential flow filtration." The Examiner does not contend, nor can it be reasonably asserted, that Sallusto discloses enrichment of dendritic cell precursors by tangential flow filtration. Moreover, the Examiner has provided no legal basis to support the position that the recited source of enriched dendritic cell precursors can be ignored in a process claim. As set forth above, each and every limitation in the claim must be considered. While an exception to this rule has been made in the case of product-by-process claims (*see* MPEP. at § 2113), such an exception has not been made by the courts with respect to "process-by-process" claims. Accordingly, with respect to the process claims currently pending, because the Examiner has not cited to any statute or case that supports the position that the process by which dendritic cell precursors are enriched can be ignored, the tangential flow filtration limitation, as recited in claims 17 and 18, must be considered in determining novelty. For this reason, in addition to the reasons previously set forth, Applicants believe claims 17 and 18 to be novel over Sallusto.

Accordingly, for at least the reasons above, Sallusto does not anticipate claims 1, 14, 17-19, and 23 under 35 U.S.C. § 102. Withdrawal of the rejection is respectfully requested.

**Rejections under 35 U.S.C. § 103**

The Examiner maintains that claims 3, 8, 9, 13, 15, and 20-22 are unpatentable under 35 U.S.C. § 103 as follows:

Claims 3, 8, and 9 over Sallusto in view of Bernard *et al.* (*Hematol. Cell. Ther.* 40:17-26, 1998);

Claims 13 and 20-22 over Sallusto in view of Bosch *et al.* (Abstract C30, *J. Invest. Derm.*, 2001); and

Claim 15 in view of Lewalle *et al.* (*J. Immunol. Methods* 240:69-78, 2000).

Applicants again note that a *prima facie* case of obviousness requires, *inter alia*, a teaching or suggestion of each and every claim limitation in the cited art. MPEP § 2143.03. Here, for the reasons set forth above in response to the rejection under 35 U.S.C. § 102(b), Sallusto does not disclose the generation of dendritic cells from monocytic dendritic cell precursors "by culturing GM-CSF in the absence of additional cytokines." (See Bosch Declaration at ¶¶ 9-23.) None of the other cited references cure this deficiency. None of Bernard *et al.*, Bosch *et al.*, or Lewalle *et al.* disclose immature dendritic cells obtained by culturing non-activated dendritic cell precursors with GM-CSF in the absence of additional cytokines. (Bosch Declaration at ¶ 26.) The cells of both Bernard *et al.* and Lewalle *et al.* are cultured in GM-CSF in the presence of IL-4. (*Id.* (emphasis provided; citing Bernard *et al.* and Lewalle *et al.*.) Bosch *et al.* discuss conditions for obtaining mature dendritic cells. (Bosch Declaration at ¶ 14 (emphasis provided; citing Bosch *et al.*, Abstract).

For at least these reasons, the skilled artisan, reading Sallusto in view of any one or more of Bernard *et al.*, Bosch *et al.*, and Lewalle *et al.*, would not have been led to the invention as presently claimed. (Bosch Declaration at ¶ 26.) Accordingly, claims 3, 8, 9, 13, 15, and 20-22 are patentable over Sallusto in combination with any one or more of these references. Withdrawal of the present rejections under 35 U.S.C. § 103 is respectfully requested.


CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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